# Flexible sigmoidoscopy screening for colorectal cancer

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## Abbreviations

| | | |
|---|---|---|
| BRAF | - | v-raf murine sarcoma viral oncogene homolog B |
| CI | - | Confidence interval |
| CIMP | - | CpG island methylator phenotype |
| CIN | - | Chromosomal instability |
| CpG | - | Cytosine-phosphate-Guanine |
| CRC | - | Colorectal cancer |
| DNA | - | Deoxyribonucleic acid |
| FOBT | - | Faecal occult blood test |
| HR | - | Hazard ratio |
| ICER | - | Incremental cost-effectiveness ratio |
| MEI | - | Magnetic endoscopic imaging |
| MLH1 | - | MutL Homolog 1 |
| MMR | - | Mismatch repair |
| MSI | - | Microsatellite instability |
| MSS | - | Microsatellite stable |
| NORCCAP | - | Norwegian Colorectal Cancer Prevention trial |
| NordICC | - | Nordic-European Initiative on Colorectal Cancer |
| PLCO | - | Prostate, Lung, Colorectal and Ovarian cancer screening trial |
| RR | - | Rate ratio |
| SCORE | - | Screening colon rectum |
| SSA/P | - | Sessile serrated adenoma/polyp |
| TSA | - | Traditional serrated adenoma |
| UK | - | United Kingdom |
| US | - | United States of America |
| WHO | - | World Health Organization |

## Acknowledgement

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Kristiansand, November 2014

Øyvind Holme

## List of papers

Paper I:

**Effect of Flexible Sigmoidoscopy Screening on Colorectal Cancer Incidence and Mortality**
**A Randomized Clinical Trial**

*Øyvind Holme, Magnus Løberg, Mette Kalager, Michael Bretthauer, Miguel A. Hernán,, Eline Aas, Tor J Eide, Eva Skovlund, Jørn Schneede, Kjell Magne Tveit, Geir Hoff*

JAMA 2014;312:606-615

Paper II:

**Long-term risk of colorectal cancer in individuals with serrated polyps**

*Øyvind Holme, Michael Bretthauer, Tor J Eide , Else Marit Løberg, Krzysztof Grzyb, Magnus Løberg, Mette Kalager, Hans-Olov Adami, Øystein Kjellevold, Geir Hoff*

GUT, epub ahead of print
http://gut.bmj.com/content/early/2014/11/10/gutjnl-2014-307793.short?rss=1

Paper III:

**Magnetic endoscopic imaging versus standard colonoscopy in a routine colonoscopy setting: a randomized, controlled trial**

*Øyvind Holme, Ole Høie, Jon Matre, Asbjørn Stallemo, Kjetil Garborg, Audun Hasund, Håvard Wiig, Geir Hoff, Michael Bretthauer*

Gastrointestinal Endoscopy 2011;73:1215-22

# 1 Background

Colorectal cancer (CRC) is the third most common cancer in the world[1] and the second most common cancer in Norway (figure 1).[2] About 3,800 Norwegians are diagnosed with CRC each year, and approximately 1,600 die from the disease.[3] Mortality rates have been quite stable the last 50 years, but incidence rates in Norway have been steadily increasing (figure 2).[2] The reason for this incline in CRC incidence is unknown.

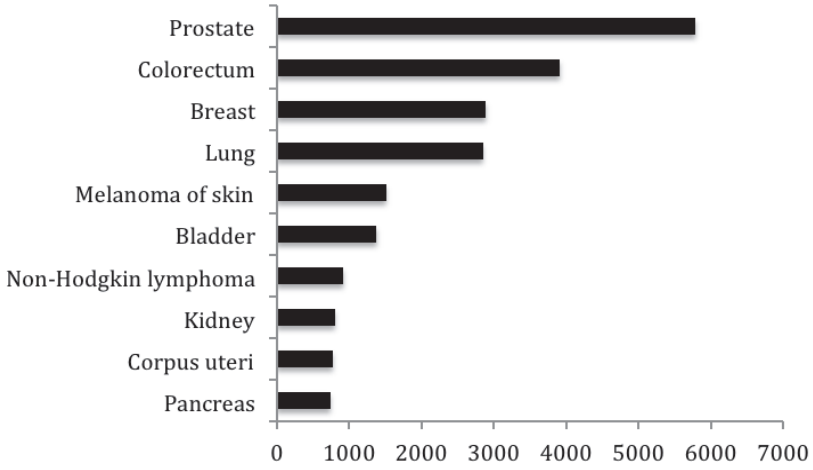


*Figure 1: Estimated numbers of the 10 most frequent cancers except non-melanoma skin cancers in Norway (2012).*[2]

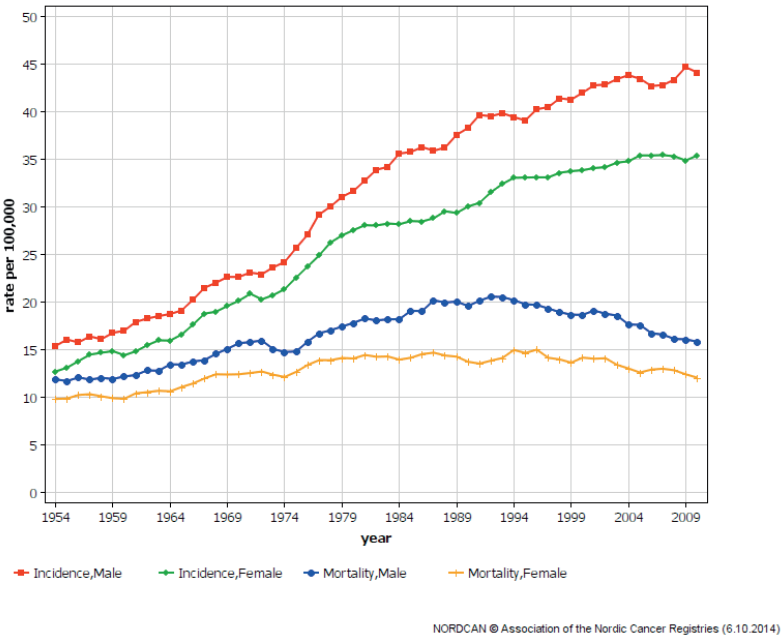


*Figure 2: Time trends in Norway for colorectal cancer incidence and mortality in men and women.[1] Rates are age-standardized per 100,000 person-years.*

Known risk-factors for CRC are increasing age, male sex, inflammatory bowel disease, prior personal history of CRC or adenomas, first-degree relatives with CRC, a diet high in fat or low in fiber, calcium or both, smoking, high alcohol consumption, sedentary lifestyle and some genetic disorders.[4,5] Regular use of aspirin, non-steroidal anti-inflammatory drugs and the use of hormone-replacement therapy have been suggested as protective factors.[4] Because CRC is considered a major health burden, screening for CRC has been implemented in many countries.[6,7]

According to the World Health Organization (WHO), screening is "…the presumptive identification of unrecognized disease or defect by the application of tests, examinations or other procedures…".[8] The WHO lists a number of prerequisites which should be met for a disease to be suitable for screening, including:

- The disease should be an important health problem
- Treatment for the disease should be accepted

- The natural history of the disease should be adequately understood
- There should be a recognizable latent or early symptomatic stage
- There should be a suitable test or examination
- The test should be acceptable to the population

For CRC, all criteria concerning the disease are met: CRC is frequent in the population (the lifetime risk in the general population is about 5%), treatment most often involves a surgical procedure, and most CRC cases develop from benign precursors; adenomas, which may be detected endoscopically. The present thesis investigates whether flexible sigmoidoscopy is a suitable and acceptable colorectal cancer screening test.

The association between colorectal cancer and adenomas has been known for a long time,[9] and the development from adenoma to carcinoma (adenoma-carcinoma sequence theory) was described further by Muto in 1975.[10] In 1988, Vogelstein proposed that this sequence was a result of a series of DNA mutations.[11] That CRCs may bleed and that this blood can be detected in stool was known already in the 18th century, but detection of faecal occult blood was not feasible as a mass-screening method until the 1960s when a guaiac-based kit for use at patients' home was introduced.[12]

The first large randomized controlled trial of screening for faecal occult blood to reduce mortality and incidence of colorectal cancer was launched in the United States in 1975. [13] Soon thereafter, researchers in several European countries initiated three randomized trials comparing screening with biennial faecal occult blood test (FOBT) to no screening. These studies found that screening with FOBT biennially or annually reduce mortality from colorectal cancer by 15-33%.[13-16] It was, however, evident from meta-analyses of these trials that FOBT did not reduce incidence of CRC. [17,18]

## *1.1 How screening works*

Screening may reduce the burden of CRC in two different ways, by early detection or by prevention (figure 3).

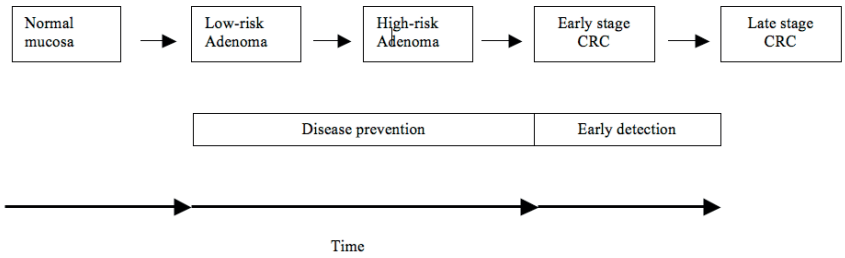


*Figure 3: How screening works. Screening may reduce the burden of CRC in two different ways; by prevention (detection, and removal, of precursor lesions to avoid development of the disease) and by early detection (detection of the disease in a stage with favorable prognosis).*

The prognosis of CRC is closely related to disease stage at diagnosis.[19] By detecting CRC at an early stage, treatment might be curable and mortality might be reduced. Detecting CRC earlier, however, will not reduce incidence. FOBT is an early-detection test, that is, a test that only detects the *disease* (a tumor which has already become malignant). The abovementioned randomized controlled trials used guaiac-based FOBT's. This test has a sensitivity for CRC precursors (advanced adenomas) of 11-25%,[4] which explains the lack of effectiveness on CRC incidence. It should be noted that one of the FOBT trials, the Minnesota trial, showed an effect on CRC incidence, but in this trial, 38% of participants screening annually and 28% of those screened biennially had a colonoscopy[13] compared to less than 10% in the other three FOBT trials.[14-16] During colonoscopy, adenomas may be detected and removed.

Screening may reduce CRC incidence (and as a consequence also mortality) by disease prevention if the applied test is able to detect benign CRC precursors (adenomas). In 1974, Gilbertsen published a report of 18 000 patients from Minnesota who had periodic

examinations with a rigid proctosigmoidoscope.[20] If adenomas were detected during the examination, they were removed. After 25 years, the numbers of distal colorectal cancers in these patients were 85% lower than in the background population of Minnesota, suggesting the possibility that screening with excision of adenomas would reduce incidence of CRC, and subsequently mortality from CRC. Several subsequent case-control studies supported this finding.[21,22]

The introduction of flexible endoscopes made the examination easier for the endoscopist and less uncomfortable for the patient, and a great technological breakthrough was achieved in the 1980s with the introduction of the videoendoscope which allowed the endoscopic image to be displayed on a screen beside the examination table.[23]

## *1.2 Flexible sigmoidoscopy*

Endoscopy with flexible endosscopes was introduced in the 1960s.[24] Sigmoidoscopy is the visual inspection of the mucosa of the rectum and the distal colon (sigmoid colon and sometimes including the descending colon). The flexible endoscope used for the examination has a working channel, which allows introduction of instruments for both diagnostic and therapeutic procedures. Flexible sigmoidoscopy has several advantages: It takes on average less than 10 minutes to complete the procedure, only an enema is required for bowel cleansing, can be performed without sedation, is well accepted by patients and entails a low rate of serious complications.[25-27].

The most important shortcoming of flexible sigmoidoscopy is that only the distal part of the colorectum is examined. About 60% of CRC cases arise in this part of the colon,[28] which means that 40% of CRC cases develops in the part of the colon beyond the reach of a sigmoidoscope (proximal colon). To detect advanced neoplasia (CRC or adenomas with diameter 10 mm or larger, with villous histology or high-grade dysplasia) in the proximal colon, patients may be referred for colonoscopy if an adenoma is detected at flexible sigmoidoscopy. Whether individuals with any adenoma or only those with advanced adenomas (adenomas with diameter 10 mm or larger, with villous histology or high-grade dysplasia) should be offered colonoscopy has been debated[29] and is important both with regard to costs and risk of complications. In one study of individuals with one or more adenomas detected in the rectosigmoid, a higher prevalence of synchronous proximal

advanced neoplasia was found than in individuals without distal adenomas, irrespective of the characteristic of the distal adenoma.[30] Another study found that only individuals with advanced distal adenomas have a higher prevalence of proximal advanced neoplasia compared to individuals without adenomas in the rectosigmoid.[31] As a consequence of this uncertainty, randomized controlled trials of flexible sigmoidoscopy screening have applied different criteria for colonoscopy-referral after the screening examination.[32-35]

However, even with normal findings at flexible sigmoidoscopy, some individuals will have a proximal advanced neoplasia: About 50% of individuals with proximal advanced neoplasia don't have a distal adenoma.[30,36]

A recent study showed that also about 50% of proximal serrated polyps (another type of polyp which may be CRC precursor, see section 1.3) did not have a distal polyp (adenoma or serrated) that could trigger a full colonoscopy, [37] further adding to the limitation of flexible sigmoidoscopy as a cancer prevention tool.

The effectiveness of flexible sigmoidoscopy- and FOBT-screening on CRC mortality has never been directly compared in randomized controlled trials. In a Cochrane-review, the two tests were indirectly compared in a multiple-treatment meta-analysis.[18] The risk of dying from CRC was 15% lower with flexible sigmoidoscopy screening compared to annual or biennial FOBT-screening (guaiac-based tests), but the difference was not statistically significant (relative risk 0.85, 95% Credibility Interval 0.71-1.01). In Norway, a screening pilot trial has been launched which directly compares flexible sigmoidoscopy to biennial FOBT (immunochemical test). In this trial, 140,000 individuals aged 50-74 years will be randomized to be invited to flexible sigmoidoscopy or biennial FOBT.[38]

Colonoscopy with complete examination of the colorectal mucosa has the ability to overcome the inherent shortcoming of flexible sigmoidoscopy. In the US, colonoscopy is the most common screening test.[39] Evidence for colonoscopy as a screening tool is however derived from flexible sigmoidoscopy screening trials and observational studies which do not take into account complications and compliance with screening. There are several large ongoing randomized controlled trials that evaluate the effectiveness of colonoscopy screening on colorectal cancer incidence and mortality.[40-43]

## *1.2 Flexible sigmoidoscopy screening trials*

The first randomized controlled trial of flexible sigmoidoscopy screening versus no screening was launched in Telemark County, Norway, in 1983. This small study included only 799 patients randomized to flexible sigmoidoscopy screening or no screening, but with a high compliance rate of 81%. After 13 years, CRC incidence was reduced by 80% in an intention-to-treat analysis.[44] In the1990s, large randomized controlled trials of screening sigmoidoscopy versus no screening were initiated in the United Kingdom, Italy, the United States, and Norway. [32,33,45,46] Long-term follow-up results have been published from the first three trials,[32-34] and short term follow-up of part of the trial cohort in the Norwegian (NORCCAP – Norwegian Colorectal Cancer Prevention) trial.[45] Long-term follow-up in the NORCCAP trial is part of this PhD thesis and will be discussed in detail later (paper I).[35] The results from the three previous trials were consistent in reduction of CRC incidence (18% - 23%) and CRC mortality (22% - 31%).[32-34] A distinguished feature of the NORCCAP trial lies in the design of the trial. While participants in NORCCAP were randomized directly from the population registry (post-randomization consent), the three other flexible sigmoidoscopy trials recruited volunteers (pre-randomization consent). This might have resulted in estimates that do not reflect the effect of the screening intervention in the entire population. Further advantages of the NORCCAP trial are inclusion of a younger age-cohort (50-54 years) than the other trials, and the absence of contamination by concurrent CRC screening outside the trial. Screening as indication for colonoscopy is infrequent in Norway.[47]

## *1.3 Serrated polyps*

For many years, the most common polyps of the large intestine were divided into two main categories; adenomas and hyperplastic polyps. Hyperplastic polyps were considered to have no malignant potential, and adenomas were considered to be the only precursors to CRC.[48] But there were reports which were not compatible with this theory: Hyperplastic polyps were found more frequently in individuals with CRC compared to those without CRC.[49] Cases were described with CRC occurring in polyps with mixed hyperplastic and adenomatous morphology,[50] and large hyperplastic polyps were described, indicating the potential of growth.[51] In 1996, Torlakovic and coworkers described increased risk for CRC in individuals with so called hyperplastic polyposis

(multiple large hyperplastic polyps), and found morphologic features which distinguished hyperplastic polyps in polyposis patients from diminutive hyperplastic polyps found in patients without hyperplastic polyposis.[52] In 2003, Goldstein published a histologic analysis of a series of lesions diagnosed as hyperplastic polyps in patients who later developed CRC in the same anatomic bowel segment.[53] These polyps were morphologically identical to the polyps described by Torlakovic and suggested that also non-adenomatous polyps could be precursors for CRC.

Today, the type of polyps Torlakovic and Goldstein described is known as sessile serrated adenoma/polyp (SSA/P). They are a subtype of a group of polyps called serrated polyps, which in addition to SSA/P consists of hyperplastic polyps and the rare traditional serrated adenomas (TSA).[54]

There are three established molecular CRC pathways;

- the chromosomal instability pathway (CIN),[55]
- the microsatellite instability pathway (MSI)[56]
- the CpG island methylator phenotype pathway (CIMP), also called the serrated pathway.[57]

A tumor may exhibit features from more than one of these pathways.[55] About 70-80% of CRC cases develop from adenomas, mostly through the CIN pathway which is characterized by imbalance in chromosome number and loss of heterozygocity.[55] Adenomas are thought to be the precursor of CRC with CIN. MSI is characterized by loss of DNA mismatch repair activity. About 15% of CRC exhibit MSI which may be caused by either germ-line mutation in one or several of the mismatch repair (MMR) genes (Lynch syndrome), or by hypermethylation of the promoter region of the *MLH1* gene (an MMR gene).[56] Hypermethylation of CpG islands (CIMP-high) is the key feature of tumors of the serrated pathway. CpG islands (repetitive sequences of cytosine and guanosine nucleotides) are found in promoter regions of about half of all genes. Aberrant hypermethylation of these regions may silence the downstream gene. CIMP may lead to CRC by methylation of the promoter region of *MLH1*, causing CIMP-high MSI tumors, or by silencing tumor suppressor genes, causing CIMP-high microsatellite stable (MSS) tumors.[56,57]

CIMP is found in both adenomas[58] and serrated polyps,[59] but more frequently in the latter. BRAF-mutations (often found in CIMP high tumors) are found in serrated polyps, but seldom in adenomas.[58,59] Thus, on this basis, serrated polyps (and in particular SSA/P) are thought to be the main precursors of CIMP-high CRC.

Little is known about the natural history of serrated polyps, but SSA/P is now believed to be a CRC precursor, and excision of these lesions is recommended in updated guidelines and a consensus statement both in the US and in Europe. [60-62] However, these guidelines acknowledge that the recommendations are based on low-quality evidence, and further research is warranted.

At the time the NORCCAP trial was conducted, all non-adenomatous polyps were diagnosed as hyperplastic polyps (WHO criteria of 2000) and were not considered to be CRC precursors. Thus, patients with these polyps were not recommended surveillance according to the Norwegian postpolypectomy guidelines (the surveillance guidelines used in NORCCAP).[63] In addition, the treatment of polyps which macroscopically appeared to be non-adenomatous was not uniform in NORCCAP. Some were removed by endoscopic polypectomy, and some were left in-situ after biopsy suggested non-adenomatous histology. This gave us the opportunity to study the natural history of serrated polyps. The NORCCAP trial also gave us the opportunity to assess the risk of CRC in individuals with serrated polyps compared to individuals with other kind of polyps detected at screening (paper II).[64]

## *1.4 Pain during endoscopy*

Colonoscopy (with polypectomy if appropriate) is the cornerstone for investigation of any positive CRC screening test. As screening involves examination of asymptomatic, and most often healthy, individuals, it is particularly important to avoid complications and discomfort. If the screening procedure (including colonoscopy) is considered to be uncomfortable, it may affect screening compliance.

Colonoscopy may be an uncomfortable and even painful procedure.[65,66] Several methods to reduce colonoscopy discomfort have been introduced, including thinner endoscopes,

endoscopes with variable stiffness, carbon dioxide insufflation and installation of water during insertion.[67-70]

Pain during colonoscopy is caused by stretching of the mesentery, which is caused by looping of the instrument, most often when the sigmoid colon is negotiated.[71] The endoscopist is often unaware of the type of looping that has occurred.[72] To avoid looping of the instrument, and to facilitate correct maneuvers to un-loop the endoscope, and thereby reduce pain, external imaging of the endoscope's configuration within the abdomen might reduce patient's discomfort.

In the beginning of the endoscopy-era, colonoscopy without the aid of fluoroscopy (the use of x-ray to visualize the intraabdominal position of the endoscope) was not considered appropriate,[24] but as technique improved, many colonoscopists abandoned fluoroscopy. Radiation exposure and large investment costs and thus inaccessibility were important arguments in a US survey of why endoscopists did not use fluoroscopy.[73] In Norway, however, fluoroscopy has been widely accepted as an important aid in difficult colonoscopies and is available in many endoscopy units throughout the country. Unfortunately, the view of the abdomen is limited, and due to radiation hazard, fluoroscopy should only be used a few seconds at a time.

In 1993, a three-dimensional magnetic endoscopic imaging system (MEI) as an alternative to fluoroscopy was described.[74] This system allows a continuous view of the position of the endoscope during the entire examination without any radiation hazard. MEI was shown to improve caecum intubation rate[75,76] and shorten time to reach the caecum[75] in prospective trials compared to colonoscopy without any external imaging, but the effect of MEI on patient's discomfort was inconsistent.[75-79] Further, the MEI is expensive, and before new devices are introduced in clinical practice, it should be tested against the best existing equipment. Colonoscopy with MEI has not been compared to colonoscopy with the aid of fluoroscopy. It is therefore unknown if colonoscopy performance improves with the addition of MEI in endoscopy units who already have access to fluoroscopy. In paper III, we report results from a randomized controlled trial, comparing MEI-aided colonoscopy to colonoscopy with fluoroscopy on-demand.[80]

## *1.5 Summary*

CRC is a common malignancy. Due to its detectable precursor state, the disease may be preventable. If a national CRC screening program is implemented in Norway, all healthy individuals in the targeted age-range will be invited for screening. Many individuals will be referred for colonoscopy (or colonoscopy may be chosen as the primary screening test), and methods to reduce discomfort should be investigated. It is important to provide policy-makers with high-quality evidence from randomized controlled trials to guide decision-making on screening and whether investment in new equipment should be performed. The reports from the NORCCAP trial and the magnetic imager trial included in this thesis provide such evidence. In recent years, it has become evident that there are several types of polyps that may be CRC precursors and which may be detected through screening. Much is unknown about these serrated polyps, and evidence from prospective trials is scarce. In the following sections, I will provide results from analyses and follow-up of individuals with large serrated polyps identified in the NORCCAP trial.

# 2 Aims

The thesis *"Flexible sigmoidoscopy screening for colorectal cancer"* investigates flexible sigmoidoscopy as a screening tool for colorectal cancer in a broad sense.

Specifically, the aims of this thesis are:

1. To investigate the long-term effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality in a population-based randomized controlled trial
2. To investigate the risk of CRC in individuals with large, serrated polyps detected at flexible sigmoidoscopy screening.
3. To investigate whether colonoscopy with the aid of a magnetic endoscopic imaging system is less uncomfortable than standard colonoscopy with fluoroscopy on-demand in a randomized controlled trial

# 3 Material and methods

## *3.1 The NORCCAP trial (paper I)*

### 3.1.1 Participants

In November 1998, individuals aged 55-64 years living in the city of Oslo or Telemark County (figure 4) were identified through the Population Registry and were eligible for the study. An equal number of men and women born between 1935 and 1945 were randomly sampled to be invited for screening (screening arm).[81] After sampling, these individuals were randomized 1:1 to receive an invitation for once only flexible sigmoidoscopy screening or to a combination of once only flexible sigmoidoscopy screening and faecal occult blood testing (FOBT) (figure 5). An independent body (IBM Norway) performed both randomization procedures using computer-based algorithms. The remaining individuals in the same age-group in the screening areas served as controls (control arm). Controls were unaware of their status as participants in the study and were not offered any intervention.


*Figure 4: The screening trial was conducted in Oslo city and Telemark County*

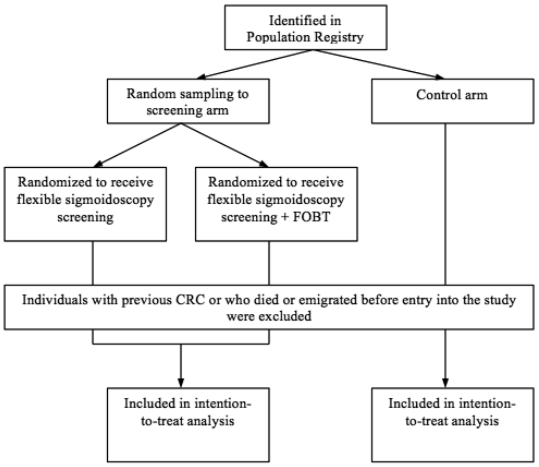


*Figure 5: Flow chart of the NORCCAP screening trial*

Based on data from the Norwegian Cancer Registry, there was an expected accumulated CRC incidence of 1% during a 5 year period (180 cases per 100,000 person years) in the 60-69 years age group. Assuming 70% compliance to detect a 30% reduction in CRC incidence (intention-to-treat analysis) after 5 years with 90% power and a significance level of 5%, 14,000 individuals had to be included in the screening arm and 42,000 in the control arm.[45] At the end of the year 2000, the funding bodies (Norwegian Government and the Norwegian Cancer Society) decided to expand the trial and also include individuals aged 50-54 years (born 1946-1950) in the trial. The rationale for this extension was to obtain more information about the ideal age to start screening. No separate power calculation was conducted for this extension of the trial. The random sampling from the Population Registry and randomization to screening with flexible sigmoidoscopy or flexible sigmoidoscopy + FOBT was done by IBM Norway in the same way as for the 55-64 year age-group. The trial was registered at ClinicalTrials, identifier NCT00119912 (available at http://www.clinicaltrials.gov).

All individuals in the trial were assigned a personal study entry date into the trial. For the individuals in the screening arm, this was the date for their proposed examination date in the invitation letter. Individuals in the control arm were assigned an entry date evenly distributed between January 1st 1999 and December 31st 2000 for controls in the 55-64 year age-group, and between January 1st and December 31st 2001 for the 50-54 year age-group. The only exclusion criterion in the trial was a personal history of CRC before

study entry. As randomization was done up to two years before invitation (date of invitation served as study entry date), individuals who died, were diagnosed with CRC or emigrated before individual study entry were excluded from the analyses (figure 5). The number of individuals included in the screening group (50-54 year age-group) was restricted by the capacity of the screening centers. Due to higher birth rates after world war II, the screening:control ratio was 1:5.4 in the 50-54 year age-group (born 1946-1950) compared to 1:3 in the 55-64 year age-group. As the population number in Oslo was higher than in Telemark, the screening:control ratio was 1:6.1 in Oslo and 1:1.5 in Telemark, see table 1.

*Table 1: Number of individuals included in the screening group and control group by age-group and screening center.*

| | 55-64 years | | 50-54 years | |
|---|---|---|---|---|
| | Screening group | Control group | Screening group | Control group |
| Telemark | 6,847 | 6,868 | 3,467 | 8,308 |
| Oslo | 6,805 | 34,221 | 3,453 | 28,823 |
| Total | 13,652 | 41,089 | 6,920 | 37,131 |

### 3.1.2 Intervention

Individuals in the screening arm were invited for screening by mail. Individuals were excluded from the examination, but included in the intention to treat analysis, if they met any of the predefined exclusion criteria. These were: 1) Previous open colorectal surgery, 2) Need for long term attention and nursing services, 3) Ongoing cytotoxic treatment or radiotherapy for malignant disease, 4) Severe chronic cardiac or pulmonary disease, 5) Patients with heart valve replacement on lifelong anticoagulant treatment, 6) Admission

to hospital for a coronary event during the previous three months, 7) Cerebrovascular accident during the previous three months, and 8) Residence abroad.

Individuals in the screening arm were invited to once only flexible sigmoidsocopy screening or a combination of once only flexible sigmoidoscopy and once-only FOBT. The FOBT kit (FlexSure OBT®, Beckman-Coulter, Palo Alto, CA, USA) was sent by mail, and individuals were asked to complete one sample from three consecutive stools and to deliver the tests on arrival at the screening examination. There were no dietary restrictions. FlexSure OBT is a qualitative immunochemical faecal occult blood test, and the tests were analyzed by the endoscopy nurse at the screening center before the endoscopic examination. Choosing only the FOBT was not an option.
The flexible sigmoidoscopy screening examinations were conducted at two screening centers, one in each of the two trial areas (city of Oslo, Porsgrunn in Telemark County). In addition, a temporary screening unit was established at Rjukan hospital in the most rural parts of Telemark for four weeks each year (1999-2001), to screen the population in these most remote parts of the screening area. This center was staffed by the same endoscopists and endoscopy nurses as the main screening center in Telemark.

Ordinary colonoscopes were used for both the screening flexible sigmoidoscopy and endoscopic work-up (140 cm Olympus colonoscopes, Olympus Europa GmbH, Hamburg, Germany) except from the temporary established screening unit (Rjukan) at which a disposable endoscopy sheath system was used (Endosheath®, Vision Sciences, Natick, MA, USA).[82]

Bowel cleansing was limited to a 240 ml sorbitol enema given at the screening center prior to the examination. During the flexible sigmoidoscopy, all detected lesions were biopsied and sent for histopathological examination. A positive screening test was defined as any polyp 10 mm or larger, any histologically verified adenoma, carcinoma or a positive FOBT. All persons with a positive screening examination were referred for colonoscopy. During colonoscopy, all detected adenomas were removed and retrieved for histopathological examinations. Treatment of non-adenomatous polyps was by the discretion of the endoscopist: Most were removed by polypectomy, while some were biopsied only. Specimens were examined by dedicated and trained pathologists: Workshops were held for the participating pathologists to ensure conformity in diagnosis,

and a referent pathologist performed blinded revision of a sample of retrieved specimens.[81] When the colorectum was considered free of all lesions (with the exceptions mentioned above), individuals with the following conditions were advised to have a surveillance colonoscopy according to Norwegian postpolypectomy guidelines. A prerequisite for these guidelines is that all polyps ≥ 5 mm in diameter has been removed, no suspicion of inherited genetic disorders with increased risk of CRC, no methodological flaws (e.g. inadequate examination, incomplete polypectomy, inadequate histopathology report) and that general health and life expectancy of the patient is reasonable.[63]

1) Surveillance after 5 years
    a. Three or more adenomas removed
    b. Only biopsy of adenoma (i.e. inadequate removal)
    c. Adenoma(s) removed and personal history of gynecological cancer
    d. Adenoma(s) removed and having a first degree relative with CRC
2) Surveillance after 10 years (if none of the criteria for 5-year surveillance have been met and there was:
    a. Adenomas with villous components
    b. Adenomas with high-grade dysplasia
    c. 1-2 adequately removed adenomas ≥ 10 mm in diameter

### 3.1.3 Definition of endpoints

Primary study endpoints were CRC incidence and CRC mortality. Outcome data were obtained from the Cancer Registry and Cause of Death Registry. In addition, data on emigration was obtained from the Population Registry.

## *3.2 Serrated polyp study (paper II)*

### 3.2.1 Participants

All included individuals in the control and screening arm in the NORCCAP trial were included in the serrated polyp study. We classified individuals in the screening arm into five groups according to screening compliance and findings at screening. For the purpose of this study, "screening" includes the flexible sigmoidoscopy screening and the colonoscopy of screen positive individuals.

1. *Non-complier group:* Individuals invited for screening who did not attend the screening examination.

2. *Non-advanced adenoma group:* Individuals with 1-2 tubular adenomas < 10mm in diameter at screening and no villous components or high-grade dysplasia.

3. *Advanced adenoma group:* Individuals with 3 or more adenomas or at least one adenoma with diameter ≥10mm, or with villous features or with high-grade dysplasia at screening.

4. *Serrated polyp group:* Individuals with at least one serrated polyp with diameter ≥10mm and no advanced adenoma at screening.

5. *Polyp free group:* Individuals with neither adenomas nor serrated polyps ≥10mm at screening.

### 3.2.2 Intervention

The screening intervention (flexible sigmoidoscopy screening and colonoscopy of screen-positive individuals) has been described under "Paper I". All histologic specimens from the screening intervention in the serrated polyp group were retrieved and re-evaluated according to modern classification of serrated polyps.[54] Two experts in gastrointestinal pathology did the re-assessment separately. Results from the individual assessment were then compared, and in case of disagreement, the specimen was evaluated by the pathologists in companionship to reach consensus. In case of continued disagreement, a third expert pathologist assessed the final diagnosis.

Hospital records of all patients in the serrated polyp group were searched for endoscopy reports and histopathology reports of polyps in the colorectum. All identified specimens were retrieved and reviewed in the same way as described above.

All individuals in the serrated polyp group who were alive and had not been diagnosed with CRC by December 31st 2011 were invited for colonoscopy in September 2012. Telemark patients were examined at the hospitals in Kragerø or Skien, and patients living in Oslo were examined at Oslo University Hospital Rikshospitalet. If a polyp was found, polypectomy was performed, and subjected to histopathological evaluation as described above.

### 3.2.3 Definition of endpoints

The primary study endpoint was CRC incidence. Information of all incident cancers during the study period was obtained from the Cancer Registry of Norway. Secondary endpoints were findings at colonoscopy performed after screening.

## *3.3 Magnetic endoscopic imaging study (paper III)*

### 3.3.1 Participants

This randomized controlled trial was conducted at Sørlandet Hospital, Kristiansand, Norway, between August 10, 2007 and May 11, 2010. Eligible participants were patients older than 18 years referred for colonoscopy at the outpatient clinic and allocated to an endoscopy suite where both the MEI (ScopeGuide®; Olympus Optical Company Ltd, Tokyo, Japan) and C-bow fluoroscopy were available. Exclusion criteria were prior colonic resection, pregnancy, inability to understand written information, requirement of sedation before the start of the procedure, or implanted pacemaker or cardioverter/defibrillator. Patients allocated to the study endoscopy suite and who were eligible to participate were screened for exclusion criteria and, after provision of written informed consent, randomized by a dedicated study nurse to either standard colonoscopy with fluoroscopy on demand (standard group) or use of the MEI system (MEI group). Sealed envelopes to be drawn by the study nurse were used for randomization.

### 3.3.2 Intervention

All procedures in both groups were performed using a standard colonoscope (Olympus CF-Q160DI provided with the Olympus ScopeGuide® system, outer diameter 13.2 mm), and ambient air was used for insufflation. In the standard group, C-bow fluoroscopy was available on demand. In the MEI group, colonoscopy was performed with the aid of the MEI system. Apart from the MEI/fluoroscopy system, all procedures were performed in the same way. An analgetic (pethidin) and/or sedation with midazolam were given only on demand.

### 3.3.3 Definition of endpoints

The primary study endpoint was pain reported by the patient on a four-point Likert scale the day after the procedure. Pain-scores were dichotomized to no/slight/moderate pain or severe pain. Secondary endpoints were caecal intubation rate, procedure time, time to reach the caecum, the need for sedation/analgesia and need for assistance from a senior colleague to complete the procedure. Endpoints were obtained by questionnaires filled in by the patients and from endoscopy report forms. The seven endoscopists in the trial were categorized as experienced (more than 200 colonoscopies performed) or inexperienced (less than 200 colonoscopies performed).

# 4 Statistical methods

Analyses were conducted with SPSS version 16.0 (SPSS, Chicago, Illinois, USA) or STATA version 12 or 13 (StataCorp, College Station, Texas, USA). All tests were two-sided and $p<0.05$ was considered as statistically significant. Categorical variables were compared using chi-square statistics or Fisher's exact test. Continuous variables were tested for normality and were compared using Student's t-test or Mann-Whitney-U test as appropriate. Logistic regression models were fitted to obtain odds ratios, and goodness of fit was tested with the Hosmer-Lemeshow test.[83] Interobserver agreement was calculated with kappa statistics.

## *4.1 The Cox model (papers I and II)*

The survival analyses used in papers I and II merits more explanation: The 50-54 year and 55-64 year age-groups were merged for analyses (paper I and II). For CRC incidence, the number of person-years were calculated from the study entry-date until a diagnosis of CRC, death, emigration or December 31st 2011. For CRC mortality, the number of person-years were calculated from the study entry-date until death, emigration or December 31st 2011.

We calculated age-standardized rates for CRC incidence and CRC mortality, and for all-cause mortality. Because of the uneven ratio between screening- and control individuals in the 55-64 year compared with the 50-54 year age groups (1:3 versus 1:5.4, respectively), individuals in the control arm were on average younger than in the screening arm (56.1 and 56.9 years, respectively). As a result, a valid analysis of the trial data could not ignore the variable age group. To explain this approach, consider separately both age groups. Because of the randomized design, treatment effects are unconfounded within both the 50-54 and the 55-64 age groups. However, pooling both age groups into a single, unadjusted analysis may introduce confounding by age group. Table 2 displays the rate ratios (RR) for CRC incidence for the two age groups separately and combined. The RR of colorectal cancer incidence is 0.68 in the 50-54 year age group and 0.83 in the 55-64 year age group. However, for the two age groups combined, the

(unadjusted) RR is 0.88, which is higher than the age-specific analyses and obviously incorrect. We therefore standardized the incidence rates according to the screening group.

*Table 2: Age-specific and overall rate ratios for colorectal cancer incidence in the screening arm compared to the control arm. Both non-standardized and age-standardized rate ratios, are given. RR: Rate ratio, CI: Confidence Interval, CRC: Colorectal cancer*

| | Screening | Control | Screening | Control | RR (Non-standardized) (95% CI) | RR (Age-Standardized) (95% CI) |
|---|---|---|---|---|---|---|
| | Cases (n) | | Person-time (years) | | | |
| **CRC incidence** | | | | | | |
| 50-54 years | 40 | 315 | 69960 | 373671 | 0.68 (0.48-0.94) | |
| 55-64 years | 213 | 771 | 151469 | 454536 | 0.83 (0.71-0.97) | |
| 50-64 years | 253 | 1086 | 221429 | 828207 | 0.88 (0.77-1.01) | 0.80 (0.70-0.92) |

We used Cox proportional hazard models to estimate relative risks (hazard ratio, HR) of the endpoints in the screening arm compared to the control arm (paper I). We included age-group (50-54 vs 55-64 years) as a binary covariate because of the age-difference between the screening and control arm (the age-difference was due to different screening-control ratio in the two age-groups: if we included age as a continuous variable, the results were identical). In paper II, sex was also included as a covariate. The Cox model assumes that the ratio of the hazards in the groups that are compared is constant. For the disease-specific and all-cause mortality analyses, the proportionality assumption was met, analyzing smoothed plots of Schoenfeld's residuals.[84] The proportionality assumption was not met when the cumulative incidence curves cross as they do in our CRC incidence analyses (papers I and II), and use of the Cox-model may seem inappropriate. However, it has been argued that the hazard ratio may be interpreted as the average causal effect across the entire study period and population, an interpretation that is clinically meaningful.[85,86] It is important to be aware that in case of non-proportionality, HRs may be sensitive to time which means that different HRs may be obtained conditional on when the cut-off for end of follow-up is set (table 3).

*Table 3: Colorectal cancer incidence in the screening arm compared to the control arm (intention-to treat). The table shows hazard ratios adjusted for age with 95% confidence intervals (CI) for different time intervals from screening to end of follow-up.*

| Time from screening to follow-up | 3 years | 6 years | 9 years | 12 years |
|---|---|---|---|---|
| Hazard ratio<br>(95% CI) | 1.21<br>(0.93-1.58) | 1.01<br>(0.83-1.24) | 0.91<br>(0.78-1.07) | 0.80<br>(0.69-0.92) |

To test whether the Cox-model provided erroneous estimates in paper I, we compared the age-standardized incidence rate ratios and the hazard ratios derived from the Cox model (Table 4), using the standardized incidence rates from table 2 in paper I. As shown in table 4, the results were identical, implying that the Cox model provides valid estimates.

*Table 4: Comparison of hazard ratios obtained from the Cox-model and age-standardized incidence rate ratios in paper I. CI: Confidence interval*

| | Hazard ratio with 95% CI (Cox) | Incidence rate ratio with 95% CI (Age-standardized) |
|---|---|---|
| Colorectal cancer incidence | 0.80 (0.70-0.92) | 0.80 (0.70-0.92) |
| Colorectal cancer mortality | 0.73 (0.56-0.94) | 0.73 (0.56-0.94) |
| All-cause mortality | 0.97 (0.93-1.02) | 0.97 (0.93-1.02) |

For estimation of the effect of screening adjusted for non-compliance, we used instrumental variable estimation with the randomization indicator (randomized to screening or to no screening) as the instrument (see section 7.2).[87]

Number needed to treat (actually: to invite) to prevent one CRC diagnosis or CRC death after 10 years were calculated as the inverse of the absolute risk difference between the screening group and the control group.

We calculated the incremental cost-effectiveness ratio (ICER) by means of prevented CRC diagnosis and CRC death in a 10-year perspective. Only direct costs were considered. Total costs were calculated as the combined cost of screening and treatment for CRC in the screening arm minus the cost of CRC treatment in the control arm. The number of prevented CRC cases and CRC deaths were calculated as the expected number of CRC cases and CRC deaths minus the observed numbers. Expected numbers were calculated by multiplying the incidence and mortality rate in the control arm with the corresponding number of person-years in the screening arm. The ICER was then obtained by dividing the total costs with the number of prevented CRC cases and CRC deaths (See supplementary appendix in paper I).

# 5 Ethics

All screening attenders in paper I provided written informed consent. The NORCCAP trial was approved by the Regional Ethics Committee and the Norwegian Data Protection Authority. The trial is registered in a clinical trial database (http://www.clinicaltrials.gov, identifier NCT00119912).

The study in paper II was conducted within the framework of the NORCCAP trial. The re-invitation for colonoscopy was waived approval from the Regional Ethics Committee.

All participants in paper III provided written informed consent. The trial was approved by the Regional Ethics Committee and the Norwegian Social Science Services. The trial is registered in a clinical trial database (http://www.clincaltrials.gov, identifier NCT00519129).

# 6 Summary of papers

## *6. 1 Paper I:*

**Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality. A randomized clinical trial**

*JAMA 2014;312:606-615*

After median 10.9 years of follow-up (11.2 years in the intervention arm and 10.9 years in the control arm), 253 individuals had been diagnosed with CRC in the screening arm, and 1,086 in the control arm. CRC incidence was thus reduced by 20% in the screening arm compared to the control arm, HR 0.80 (95% CI 0.70-0.92). Seventy-one individuals had died from CRC in the screening arm, and 330 in the control arm, corresponding to a 27% reduction in CRC mortality, HR 0.73 (95% CI 0.56-0.94). CRC incidence was reduced in both the 50-54 year age-group (HR 0.68; 95% CI 0.49-0.94) and in the 55-64 year age group (HR 0.83; 95% CI 0.71-0.96). The effect on CRC incidence and mortality was comparable in the flexible sigmoidoscopy and the flexible sigmoidoscopy + FOBT screening group.

In the per protocol analyses (after 10 years of follow-up, adjusting for non-compliance), the absolute risk reduction in CRC incidence was -0.42% (95% CI -0.69% to -0.15%) as compared to -0.22% (95% CI -0.38% to -0.06%) in the intention-to treat analysis. For CRC mortality, the risk reduction was -0.10% (95% CI -0.25% to 0.05%) in the per protocol analysis and -0.06% (95% CI -0.14% to 0.03%) by intention-to-treat.

We estimated the number needed to treat and the incremental cost-effectiveness ratio after 10 years of follow- up. To prevent one CRC case, 455 individuals had to be invited for screening at a cost of $58.448 per CRC case prevented. To save one death from CRC, 1667 individuals had to be invited for screening at a cost of $226,002 per CRC death prevented.

## *6.2 Paper II:*

**Long-term risk of colorectal cancer in individuals with serrated polyps**

*GUT, epub ahead of print*
*http://gut.bmj.com/content/early/2014/11/10/gutjnl-2014-307793.short?rss=1*

This study was conducted within the framework of the NORCCAP trial (paper I). We categorized individuals in the screening arm into five groups according to screening compliance and finding at the screening examination (including follow-up colonoscopy of screen-positives) as described previously:

Compared to the individuals without adenomas or polyps ≥10 mm (polyp free group) detected at screening, individuals with large serrated polyps (serrated polyp group) had increased risk for a CRC diagnosis after median 10.9 years of follow-up, HR 4.2 (95% CI 1.3-13.3) The risk was comparable to individuals with advanced adenomas who had a HR for CRC incidence of 3.3 (95% CI 2.1-5.2) compared to the polyp-free group (P=0.7 for comparison). The risk for CRC in individuals in the serrated polyp group was larger than for individuals with non-advanced adenomas who had a HR of 1.1 (95% CI 0.6-1.9) compared to the polyp-free group (p=0.03 for comparison). Compared to the general population, the risk for CRC in the serrated polyp group was 2.5 times higher, but this result did not reach statistical significant difference, HR 2.5 (95% CI 0.8-7.7). The HR for CRC incidence for individuals with advanced and non-advanced adenoma compared to the general population was 2.0 (95% CI 1.3-2.9) and 0.6 (95% CI 0.4-1.1), respectively. Having a serrated polyp ≥10 mm was an independent risk factor for being diagnosed with CRC in a multivariate logistic regression model adjusting for age, sex and characteristics of concomitant adenomas (Odds ratio 3.3, 95% CI 1.3-8.6).

Twenty-three serrated polyps ≥10mm left in situ (only biopsied in the screening trial) for median 11 years. In none of these individuals, CRC developed in the same colon segment as the index polyp left in situ, and few polyps increased in size.

## *6.3 Paper III:*

**Magnetic endoscopic imaging versus standard colonoscopy in a routine colonoscopy setting: a randomized, controlled trial**

*Gastrointestinal Endoscopy 2011;73:1215-1222*

A total of 810 individuals scheduled for outpatient colonoscopy at Sørlandet Hospital Kristiansand between 2007 and 2010, and who were willing to start the procedure without sedation or analgesia, were randomized to examination with MEI-aided colonoscopy (n=419) or standard colonoscopy (n=391) with fluoroscopy on-demand. We found no significant difference in the proportion of patients with severe pain between the MEI-guided (12.6%) and the fluoroscopy on demand colonoscopy group (16.7%), p=0.15. The results were the same for experienced and inexperienced endoscopists.

For experienced endoscopists, we did not detect any difference in the two study arms for caecum intubation rate, time to reach the caecum, need for assistance or use of sedation/analgesia. Inexperienced endoscopists, on the other hand, had a higher caecum intubation rate (77.8% vs 56.0%, p=0.02) and less need for assistance (18.5% vs 40.0%, p=0.02) with MEI-guided colonoscopy than with standard colonoscopy. There was no difference in use of sedation/analgesia or time to reach the caecum in the two study arms for inexperienced endoscopists.

# 7 Discussion

CRC is an important health problem. In Norway, about 3800 persons were diagnosed with CRC in 2011,[2] and the disease accounted for 3.8% of all deaths in 2012.[3] As it is believed that CRC arises from benign precursors, the disease may be preventable. Screening for CRC has thus been implemented in many countries.[6,7]

## *7.1 NORCCAP compared to previous trials*

We found that CRC incidence was reduced by 20% and CRC mortality by 27% (paper I).[35] In the previously published flexible sigmoidoscopy screening trials, CRC incidence in these trials was reduced by 18-23% and CRC mortality by 22-31%.[32-34] The results are thus remarkable consistent despite the disparity in design (post- versus pre-consent randomization), the age of the individuals included in the different trials and the possible contamination of the individuals in the control arm by screening outside the trial. A meta-analysis of the four trials (using fixed-effect Mantel-Haenszel model) shows that the pooled risk ratio for CRC incidence is 0.78 (95% CI 0.75-0.83), in the screening arm compared to the control arm (figure 6).

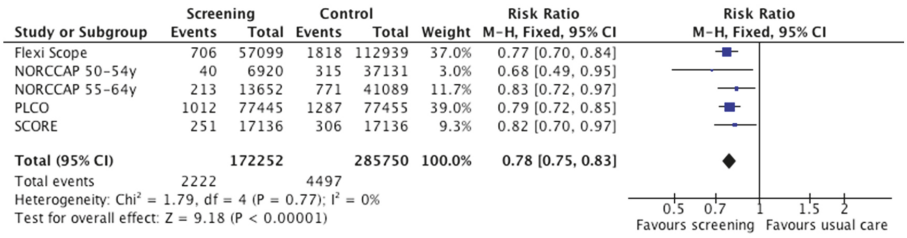


*Figure 6: Meta-analysis of CRC incidence in the four flexible sigmoidoscopy screening trials. NORCCAP: Norwegian Colorectal Cancer Prevention trial, PLCO: Prostate, Lung, Colorectal and Ovarian cancer screening trial (USA), SCORE: Screening Colon Rectum (Italy). The Flexi Scope trial was conducted in the United Kingdom.*

For CRC mortality, the pooled risk ratio is 0.72 (95% CI 0.66-0.80) in the screening arm compared to the control arm (figure 7). Most importantly, there is no statistical heterogeneity between the trials for neither CRC incidence nor mortality (figure 6 and 7: $I^2$=0%).

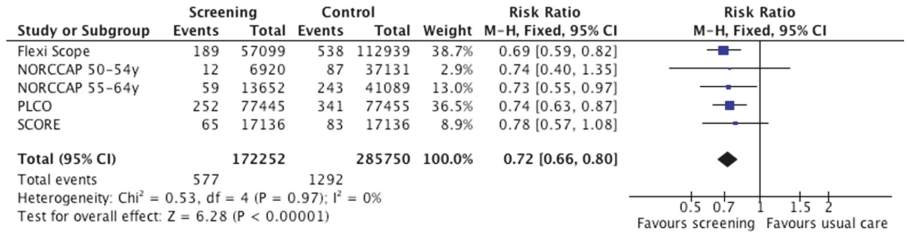


*Figure 7: Meta-analysis of CRC mortality in the four flexible sigmoidoscopy screening trials.*

It is interesting to compare the four randomized controlled trials of flexible sigmoidoscopy in terms of effect on CRC incidence in the distal versus proximal colon. It has been shown in previous trials that individuals with a distal adenoma have increased risk of proximal advanced neoplasia (defined as advanced adenoma and CRC), even if the results from these trials diverge with respect to the importance of different adenoma characteristics.[30,31,88] One might expect that the trials with the highest colonoscopy referral rate after screening reduced proximal CRC incidence the most, but there is evidence in the literature that colonoscopy may not reduce incidence of advanced proximal neoplasia or CRC [89,90] or death due to proximal CRC.[91,92]

The four flexible sigmoidoscopy trials had important differences in the threshold for referral to colonoscopy. In the NORCCAP trial, CRC, any adenoma (irrespective of size) or any polyp 10 mm or larger (or positive FOBT) qualified for colonoscopy. In the PLCO (Prostate, Lung, Colorectal and Ovarian cancer screening) trial from the US,[33] all individuals with any detected polyp or mass were referred for colonoscopy. In the UK

Flexi Scope trial, people with any polyp ≥ 10 mm, adenomas with high-grade dysplasia or villous/tubulovillous histology, multiple adenomas (three or more) or ≥ 20 hyperplastic polyps above the distal rectum or CRC were offered colonoscopy.[32] In the Italian SCORE (Screening Colon Rectum) trial, individuals with a polyp > 5 mm, adenoma with high-grade dysplasia or villous/tubulovillous histology, multiple adenomas (three or more) or CRC were referred for colonoscopy.[34] These differences led to widely varying colonoscopy rates (19.5% in NORCCAP; 5.0% in Flexi Scope; 7.8% in SCORE and 21.9% in the PLCO trial). Of note, individuals in the PLCO trial were offered two screening examinations 3-5 years apart, while only one examination was offered in the other three trials. The reduction in CRC incidence of the distal colon and rectum was comparable between the trials (24-36% with overlapping confidence intervals). The reduction in proximal CRC incidence, however, was more varying between the trials and increased as the colonoscopy rate increased, from 2% reduction in the Flexi Scope trial to 14% in the PLCO trial (a 7-fold difference, a statistically significant reduction in the PLCO trial only). This is consistent with recent observational studies that suggest a protective effect of colonoscopy also on proximal CRC incidence[93] and CRC mortality.[94]

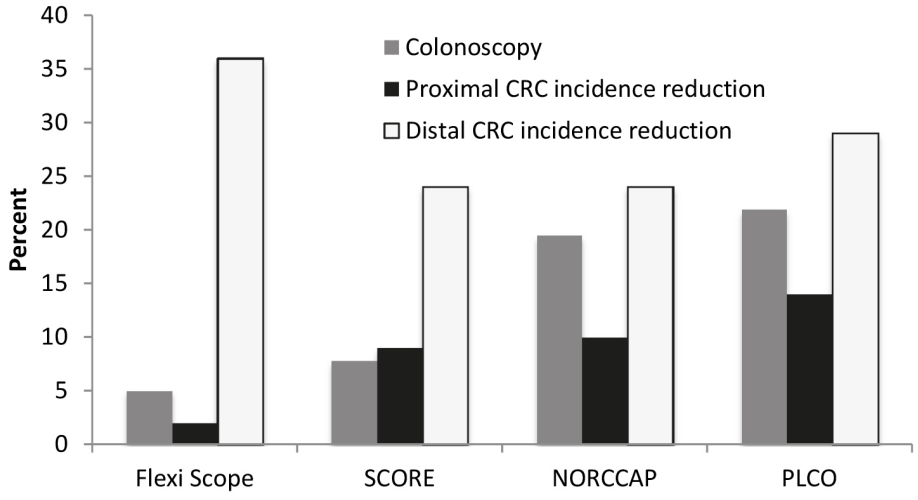


*Figure 8: Comparison of the four flexible sigmoidoscopy screening trials: Proportion of screening compliers who had a colonoscopy and relative reduction in CRC incidence in the distal and proximal colon in the screening arm compared to the control arm.*

However, even referring all individuals with a pathologic finding at flexible sigmoidoscopy screening to colonoscopy is not very efficient in reducing proximal CRC incidence and mortality.[33] About 70% of advanced adenomas in the entire colon and rectum are detected if individuals with any adenoma at screening flexible sigmoidoscopy are referred for colonoscopy.[95] About 50% of individuals with proximal advanced neoplasia do not have a distal adenoma which could trigger a full colonoscopy, and in a recent study, it was shown that 52% of proximal advanced serrated polyps (TSA, SSA/P with dysplasia, SSA/P with size ≥10mm in diameter) do not have a distal polyp.[30,37]

In the Spanish COLONPREV-trial, a randomized trial comparing colonoscopy to biennial faecal immunochemical testing (FIT), the baseline findings from the colonoscopy screening arm or colonoscopy crossover from the FIT-arm (total n=5059) were used to simulate different yield of proximal or any advanced neoplasia according to the different colonoscopy referral criteria in NORCCAP, SCORE and Flexi scope.[40,96] The detection rate of any advanced neoplasia at colonoscopy in COLONPREV was 10.3%. If the Flexi Scope, SCORE or NORCCAP criteria for colonoscopy were applied, the detection rates were only modestly different; 6.3%, 6.7% and 7.0%, respectively, although the differences reached statistical significance.[96] Colonoscopy referral rates, when the different criteria were applied to the COLONPREV-participants, were 6.2%, 12.0% and 17.9%. Accordingly, a three-fold increase in colonoscopy-referral rate (from 6.2% to 17.9%) increased the sensitivity for detection of any advanced neoplasia only from 61% (317/520) to 68% (355/520). The sensitivity for detection of any proximal advanced neoplasia was 22%, 31% and 37%, respectively. Of note, only 1 of 6 proximal CRC in the COLONPREV trial would have been detected by screening sigmoidoscopy, regardless of referral strategy.

Interestingly, having isolated proximal advanced neoplasia/adenoma has been suggested to be more common amongst women than men.[97,98] This may be the reason why we in the NORCCAP trial found a smaller, though not statistically significant, effect on CRC mortality and incidence in women than in men. Also the PLCO trial reported a lower effectiveness of flexible sigmoidoscopy screening in women than in men, but the difference did not reach statistical significance.[33] On the other hand, in the SCORE trial, women had a larger reduction in CRC incidence than men (not statistically significant), but is also the smallest of the four trials.[34] In the abovementioned COLONPREV simulation study, the sensitivity for detection of advanced proximal neoplasia was

significantly lower in women than men, regardless of colonscopy referral criteria.[96] Taken together, these results suggest that there may be a difference in effectiveness of flexible sigmoidoscopy screening between men and women and should be explored further. It would be very interesting to perform a meta-analysis stratified by sex of the four trials.

The age at when to start screening has not been firmly established. US guidelines recommend starting at 50 years,[7] but evidence for this recommendation from randomized controlled trials is limited. The NORCCAP trial included individuals from 50 years of age, while the other three trials included individuals 55 years and older. Our results show that flexible sigmoidoscopy screening reduces CRC incidence also in the 50-54 year age group (HR 0.68, 95% CI 0.49-0.94). This indicates that screening for CRC should start at age 50, but it should be remembered that the age-specific results are subgroup analyses, and the results should thus be interpreted with caution.

Complications to screening should also be mentioned. Among 12 955 individuals screened with flexible sigmoidoscopy in NORCCAP, there were no complications, but detected polyps were biopsied only. There were 6 perforations (1 in 336 therapeutic colonoscopies: 0.3%) , all due to polypectomies during colonoscopy.[25] The complication rate was higher than in the three other flexible sigmoidoscopy trials. The reason for this is unknown; all the endoscopists in the NORCCAP trial were experienced. In a report from the English bowel screening program, there were 63 perforations in 69 028 therapeutic colonoscopies (0.09%, one third compared to the perforation rate in NORCCAP).[99] All the endoscopists in the English screening programme have to be accredited and undertake a written and practical examination, and quality indicators are measured continuously.[100] Educating endoscopists and continuous quality assurance surveillance is important to minimize harm in association with CRC screening.

## *7.2 Per protocol analyses*

The standard approach for analyzing data from a randomized controlled trial like NORCCAP is the intention-to-treat approach, meaning that every individual in the screening arm is included in the analysis, no matter whether they received the intervention or not. An intention-to-treat calculation will give a conservative effect estimate (biased towards the null) of the intervention when compliance is not 100%. An

intention-to-treat analysis will estimate the effect of being assigned to the intervention (e.g. invitation for screening), rather than the intervention itself. What we really want to know is the true effect of the intervention itself. Thus, we aimed at estimating the "per protocol-effect", that is, the effect of the screening intervention if everyone was compliant with the trial protocol (everyone assigned to screening attended their screening examination and no one in the control arm had a screening examination), see appendix of paper I.

Our first approach was to collect as much information about the participants (in both the control and screening arm) as possible to uncover factors that predicted compliance with screening. Using this information, we intended to perform propensity score matching/adjustment.[101] To perform such an analysis, however, we had to identify all joint predictors of compliance and the outcome (e.g. CRC incidence and mortality). Usually, this assumption is not empirically verifiable, but in the NORCCAP trial, we could test whether compliance occurred at random. If it occurred at random, then the CRC incidence rate and mortality rate would be the same in the control arm as in the non-compliers. For CRC incidence, this was indeed true. The age-adjusted HR for CRC incidence in the non-compliers as compared to the controls was 1.02 (95% CI 0.84-1.24). This means that the CRC incidence risk was similar in the non-compliers and the controls, and that the CRC incidence reduction amongst the compliers was only due to the intervention, not to selection. This gave us the opportunity to estimate the effect of the screening intervention (per-protocol effect) by fitting a Cox model comparing the compliers to the control arm. The age-adjusted HR for the per protocol effect for CRC incidence was 0.68 (95% CI 0.57-0.81) as compared to 0.80 (95% CI 0.70-0.92) in the intention-to-treat analysis..

For CRC mortality however, the HR was 1.35 (95% CI 0.99-1.85) in the non-compliers compared to controls, and was only marginally changed when we included all obtainable socioeconomic and comorbidity variables (Table 1 in the appendix of paper I). This means that controls and non-compliers are at different risk with respect to CRC mortality (35% higher among noncompliers compared to controls), and that adjustment for variables that may predict compliance is insufficient to eliminate this difference.

The results from the CRC mortality analysis indicate that all analyses which require adjustment for joint predictors of compliance and CRC mortality will be biased. This also

includes propensity score matching which was our initial intention. We thus used instrumental variable (IV) estimation to adjust for non-compliance, with the randomization indicator (randomized to screening or to no screening) as the instrument, which does not require adjustment for the joint predictors.[87]

When we consider the Directed Acyclic Graph (DAG) in figure 9, we can see that the randomization meets the three basic assumptions for an instrument:

1) Z is associated with X
2) Z affects the outcome Y only through X, and
3) There is no confounding of Z on Y

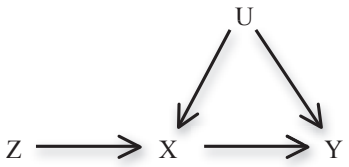


*Figure 9: Directed Acyclic Graph. Z: Randomization indicator; X: Screening intervention (flexible sigmoidoscopy); Y: Outcome (Colorectal cancer incidence or mortality); U: Unmeasured and measured confounders.*

In other words: The randomization indicator is likely to meet the three instrumental assumptions: randomization is strongly associated with attendance to screening, we expect no effect of randomization on the outcome except through screening (called the exclusion restriction), and we expect the intention to treat effect to unbiasedly estimate the effect of assignment (no confounding for the effect of the instrument).

The intention to treat risk difference between the screening arm and the control arm can be written as:

$$P(Y|Z=1) - P(Y|Z=0)$$

Where P is the probability of the outcome Y and Z is the randomization indicator. Z=1 indicates randomization to screening, and Z=0 indicates randomization to no screening (control arm).

Using Z as an instrument, we can write the per protocol effect (adjusted for non-compliance) as:[87]

$$\frac{P(Y|Z=1) - P(Y|Z=0)}{P(X|Z=1) - P(X|Z=0)}$$

where P(X|Z=1) indicates the probability of receiving the intervention conditioning on randomization to the screening arm (that is, compliance), and P(X|Z=0) indicates the probability of receiving the intervention conditioning on randomization to the control arm (that is, contamination). From the Norwegian Gastronet data, we know that screening for colorectal cancer is a rare indication for colonoscopy in Norway,[47] and there has been no organized screening for CRC in the trial period, which means that P(X|Z=0) is zero for all practical purposes. Therefore, the per protocol risk difference equals:

$$\frac{P(Y|Z=1) - P(Y|Z=0)}{P(X|Z=1)}$$

As this instrumental variable calculation is on the risk difference scale, we restricted our calculation to 10 years of follow-up. We had to apply this approach because all individuals in NORCCAP had at least 10 years follow-up. To calculate the risk, every individual in the denominator must have the possibility to be a case (e.g. diagnosed with CRC or die from CRC), that is, included in the numerator.

We calculated the intention-to-treat risk difference to be -0.22% (95% CI -0.38 to -0.06) and the IV multivariate adjusted risk difference to -0.42% (95% CI -0.69 to -0.15). For CRC mortality, the intention-to-treat risk difference was -0.06% (95% CI -0.14 to 0.03) and the IV multivariate adjusted risk difference was -0.10% (95% CI -0.25 to 0.10). This means that the estimated per protocol effect is considerable higher than the intention-to-treat estimate.

The interpretation of the per-protocol effect using instrumental variable estimation has an important limitation. In addition to the three above mentioned assumptions, our calculations were based on the assumption of monotonicity. Monotonicity indicates that we assume that there are no defiers, that is, that there are no individuals in neither the control arm nor the screening arm who will do exactly the opposite of what they were randomized to. This assumption implies that the per-protocol calculation estimates the effect of the intervention in those who would have complied with the screening invitation, and not the effect in the entire study population.

It is of interest that also the SCORE and Flexi Scope trial estimated a per-protocol effect,[32,34] but they used another method (described by Cuzick et al).[102] The reported increase in efficacy of flexible sigmoidoscopy screening in these per protocol analyses was of the same magnitude as in the univariate (age-adjusted) IV analyses of the NORCCAP data (see eTable 2 in the appendix). The method described by Cuzick is also an instrumental variable estimation with the same important limitation as outlined above.[103] For example, the per protocol (compliance-adjusted) decline in CRC mortality in the Flexi Scope trial was 43% (HR 0.57, 95% CI 0.45-0.72). This may be interpreted as the effect of flexible sigmoidoscopy screening on CRC mortality in the entire study population. But due to the assumptions mentioned above, it should be interpreted as the effect of flexible sigmoidoscopy screening among the compliers only.

### *7.3 How screening works*

Screening with flexible sigmoidoscopy may reduce CRC mortality by prevention and by early detection, but it is uncertain which of the two mechanisms that contributes the most. In NORCCAP, more CRCs were observed in the screening arm than the control arm the first year after inclusion in the trial due to screen-detected cancers. But after this first year, fewer CRCs are observed in the screening arm than in the control arm (risk ratio below 1 in figure 10). Even if the number of incident cases (CRC diagnosis) are few each year, and the confidence intervals cross 1 most of the years, these results indicate that the effect of a once only flexible sigmoidoscopy screening on CRC incidence is long lasting and may affect CRC mortality beyond the follow-up time of the trial.

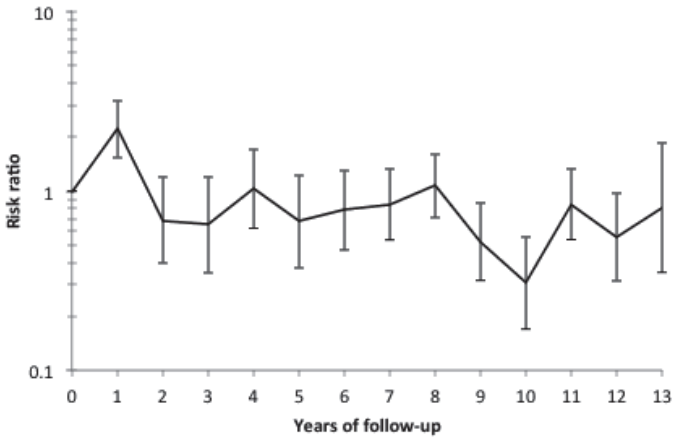


*Figure 10: Yearly risk ratio for CRC incidence in the screening arm compared to the control arm.*

Similarly, figure 11 shows the yearly risk ratio for CRC mortality in the screening arm relative to the control arm. There is a small initial reduction in CRC mortality (statistically non-significant due to few number of CRC-related deaths) already the first years after screening. This reduction is probably due to detection of less advanced cancers with a favorable prognosis at screening: 71% of screen-detected CRCs were Dukes A or B, compared to 43% in controls (Table 4 in paper I). In the first few years after screening, CRC incidence reduction is probably less important for CRC mortality as it takes some time from development from adenoma to symptomatic cancer to death. But as time from screening increases, there are fewer CRCs detected in the screening arm than in the control arm (figure 10 and figure 2 in paper I). From figure 11, the larger effect on CRC mortality evolves 9 years after screening. This probably reflects the effect of polypectomy, and the resulting decline in CRC incidence.

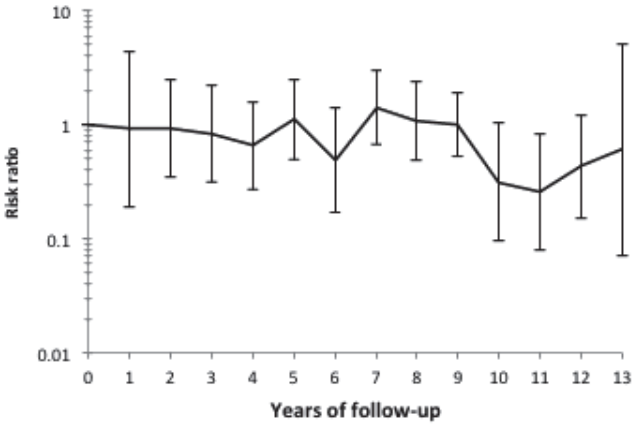


*Figure 11: Yearly risk ratio for CRC mortality in the screening arm relative to the control arm.*

Thus, the reduction in CRC mortality is caused by both early detection and prevention. It is difficult to conclude which mechanism is most important. Only 41 of 253 (17%) CRCs in the screening arm were screen-detected, but we have no information of adherence to the surveillance recommendation. Surveillance colonoscopies may have contributed to both a more favorable stage at diagnosis compared to CRCs in the control arm, but also to prevention by additional polypectomies.

## *7.4 Serrated polyps*

At the time the flexible sigmoidoscoscopy trials were conducted (1993-2001), non-adenomatous polyps were considered to have no malignant potential as stated in the 3rd edition of WHO classification of tumors in the digestive system, published in 2000.[104] Later research has, however, suggested an association of large serrated polyps with synchronous advanced neoplasia and CRC.[105,106] Very recently, a large nested case-control study from Denmark showed that the risk of metachronous CRC in individuals with SSA/P was of similar magnitude as individuals with adenomas and higher when compared to individuals without polyps.[107]

In NORCCAP, we found that 0.8% of screenees had a large serrated polyp (≥ 10mm in diameter). This is lower than other estimates which range from 1.4-2.6%.[105,106,108] This probably reflects the fact that individuals with large serrated polyps in our series were identified during flexible sigmoidoscopy, and not through colonoscopy. But the low detection rates may also be attributed to the assumption of no malignant potential for these polyps, and some polyps with appearance as hyperplastic polyps may not have been biopsied. Low detection rates may also be due to missed lesions as there is a high inter-endoscopist variation in detection of serrated polyps.[109] Variable detection rates between endoscopists for any polyp and for adenomas has been reported in the NORCCAP trial.[110]

Unlike other trials, we did not report an increased risk of synchronous CRC in patients with serrated polyps.[106] This is due to how individuals were classified. In our trial, individuals with large serrated polyps with concurrent advanced adenomas were classified in the advanced adenoma group. If we had included these 22 individuals in the serrated polyps group, 1 CRC had been screen-detected among 103 (1%) individuals with a large serrated polyp as compared to 40 CRC in all 12,852 screening attenders without a large serrated polyp (0.3%).

We found that the presence of a large serrated polyp was associated with CRC during almost 11 years of follow-up. The risk was about 4-fold compared to the risk in individuals without polyps detected at screening, HR 4.2 (95% CI 1.3-13.3). Compared to the general population, represented by the NORCCAP control arm, the HR was 2.5 (95% CI 0.8-7.7), and did not reach statistical significance. The proportion of individuals with CRC in the serrated polyp group was 3.7%. Previous retrospective studies have also suggested an association between serrated polyps and metachronuos CRC: Lu and colleagues reported on 40 individuals with non-dysplastic SSA/P. After 8-28 years, five (12.5%) developed CRC compared to 1.8% of patients with hyperplastic polyps or conventional adenomas.[111] Teriaky reported on a 5-year follow-up of 33 individuals with SSA/P or mixed SSA, and one patient (5%) developed CRC.[112] Lazarus found that 2 of 38 (5%) of individuals with dysplastic SSA/P developed CRC, but follow-up time in this study was not reported.[113] Our estimate of absolute CRC risk is lower, but direct comparison is difficult due to different time to follow-up and inclusion criteria.

We found that the risk of CRC in the serrated polyp group was comparable to individuals with advanced adenomas, HR 1.3 (95% CI 0.4-4.2) and higher compared to individuals with nonadvanced adenomas, HR 3.9 (95% CI 1.1-13.2).

We also compared the risk of metachronous CRC in individuals with advanced adenomas and serrated polyps, that is, the risk after the screening examination (excluding screen-detected CRCs from the analyses). We found that the risk of future CRC is at least as great in individuals with serrated polyps as in individuals with advanced adenomas; Hazard ratio 3.2 (95% CI 0.9-11.4). As in our primary analysis, also this analysis should be interpreted with caution as the number of CRC cases are low (indicated by the width of the confidence intervals). Another potential bias regarding this conclusion is the differences in surveillance recommendations. Eighty-five per cent of individuals in the advanced adenoma group were recommended surveillance compared to 53% of individuals with a large serrated polyp (unpublished data). However, surveillance recommendation was not an independent risk factor for metachronous CRC when this variable was included in the Cox model (p=0.8, unpublished data), and did not change the effect estimates.

It is unclear whether the increased CRC risk in individuals with large serrated polyps is confined to those whose large serrated polyp is a hyperplastic polyp or diagnosed as SSA/P.[60] We were not able to disentangle this potential difference in association for several reasons. First, we did not have enough statistical power (e.g. few CRC cases). Second, about one fifth of the serrated polyps could not be classified as either hyperplastic polyp or SSA/P. Third, multiplicity was a frequent finding in our cohort, a feature which has been associated with the serrated pathway.[114] Sixty-one per cent of individuals in our cohort had both hyperplastic polyps and SSA/P, and assessing CRC risk just based on which subgroup of serrated polyps had the largest size was not meaningful in our cohort.

The natural history of serrated polyps has previously been partly described by Lazarus, but he did not separate hyperplastic polyps from SSA/P.[113] We found that among 21 patients, harboring 23 large serrated polyps left in situ following biopsy, none of the polyps progressed to CRC, and there was modest growth during 11 years of follow-up. In a previous study of non-resected polyps > 10 mm from the Mayo clinic, the CRC risk at

the polyp site was about 1% per year (1 per 100 person-years of observation).[115] Compared to our cohort of 23 serrated polyps followed for median 11 years (about 250 personyears of observation), we should have observed at least 2 CRC cases at the site of the polyp left in situ if the risk were the same as in the cohort from the Mayo clinic, but we detected none. Again, our numbers are small, but indicate that the large serrated polyp may be a marker of increased risk of CRC elsewhere in the colon of these patients (so-called field effect), and not be the premalignant lesion itself. Another study conducted by Bouwens and colleagues reported results that were different from ours (results reported as letter only).[116] In this study, 3 out of 18 patients (17%) with proximal hyperplastic polyps larger than 5mm that were only biopsied developed CIMP-high BRAF-mutated CRC after 3, 5 and 9 years in the same colonic segment as the polyp left in situ. The reason for the discrepancy between this and our study may be that most of our large serrated polyps were located in the distal colon (14 of 23). Large proximal serrated polyps may have a different clinical course than large distal serrated polyps. Another reason may be that the polyps in our study were detected in a screening population, while patients in the Bouwen study were probably identified through diagnostic colonoscopies, even if this is not clearly stated in the report.

### 7.4.1 Field effect

We found that 63% of individuals with a large serrated polyp had a concurrent adenoma, and 21% had an advanced adenoma. Theses numbers are considerably higher than the 30% and 5.7%, respectively, found in a recent systematic review of asymptomatic individuals.[117] Further, 56% of individuals in the serrated polyp group had 3 or more serrated polyps at screening. These results indicate that serrated polyps are associated with multiplicity of both adenomas and serrated polyps, a finding also suggested by other authors.[114,118]

High level of methylation of Cytosine-rich promoter regions (CIMP-high) is associated with increasing size of serrated polyps,[59] but also with size and villousness of adenomas.[58,119] Thus, individuals with large serrated polyps may be prone to develop other serrated and adenomatous polyps, suggesting a “serrated environment” or a “field effect” in the colorectum which may be a driving force in both the adenoma-carcinoma sequence and the serrated pathway. Indeed, individuals with both serrated polyps and

adenomas may have larger serrated polyps, and larger and more advanced adenomas compared to individuals with only one type of polyp.[118] One study also described that adenomas in individuals with serrated polyps had more atypical histologic features than adenomas in individuals without concurrent serrated polyps.[120] Very recently, a study showed that 20% of CIMP-high CRCs had adenomatous polyps contiguous with the tumor, suggesting that CIMP-high tumors may evolve also from adenomas.[121]

In existing US and European postpolypectomy surveillance guidelines, serrated polyps and adenomas are treated separately.[61,62] It may be that both kinds of polyps should be considered together (the "Total polyp load") when CRC risk, and hence surveillance interval, is assessed.

Our results indicate that large serrated polyps themselves may have an indolent course. There is uncertainty in the literature how rapid the growth of serrated polyps is, and consequently, there is uncertainty to how frequent surveillance colonoscopy should be recommended. Case reports have suggested that the transition from SSA/P to CRC may be rapid.[122-125] However, a large series of 2,139 individuals with SSA/P showed that the mean age in persons with SSA/P without dysplasia was 61 years, 72 years in those with SSA/P harboring high-grade dysplasia, and 76 years in individuals with SSA/P harboring CRC, suggesting that transition from SSA/P to CRC may take 15 years.[126] In another study by Lu et al of 55 individuals with SSA/P, the mean time from detection of SSA/P to advanced adenoma or CRC was 8.3 years.[111] We found that the median time from detection of a large serrated polyp to CRC was 7.5 years, suggesting that surveillance intervals after detection of large serrated polyps may be extended beyond three years as is the current recommendations in US and European postpolypectomy surveillance guidelines.[61,62] Interestingly, only 1 of 6 advanced adenomas (n=1) or CRC (n=5) at follow-up was located in the same colon segment as the index SSA/P in the Lu study. This is consistent with our findings: Only 1 of the 3 CRCs in the serrated polyps group were located in the same colon segment as a serrated polyp found at screening. These results indicate that it may not be the polyp per se that develops into a tumor, but strengthens the theory of the field-effect, although our numbers are very small.

### 7.4.2 Limitations of the serrated polyp study

Our study of serrated polyps has several limitations, of which low statistical power due to few CRC cases is the most obvious and probably led to a statistically non-significant result when we compared the serrated polyp group to the NORCCAP control arm. Another limitation is that the polyps in our study were identified during screening flexible sigmoidoscopy. The proximal colon was not investigated in about 80% of the screening attenders. A number of these individuals may have had proximal lesions (both adenomas and serrated polyps), not detected at flexible sigmoidoscopy, and thus were classified as polyp-free. The possible bias due to this would most probably result in an underestimate of CRC risk in individuals with large serrated polyps, although an opposite effect is theoretically possible, known as the Will-Rogers phenomenon:[127] A third limitation is related to the initial classification of the large serrated polyps left in situ. This classification was based on biopsy specimens only. As the histologic differences between SSA/P and hyperplastic polyps may be subtle and unevenly distributed in the polyp, misclassification may have occurred. Thus, relation between initial diagnosis and follow-up diagnosis must be interpreted with this in mind. Fourth, our observations may be biased due to so called length-time bias.[128] As in any cross-sectional study, disease (here: polyps) with slow growth rate and good prognosis may be more frequently observed than aggressive polyps with accelerated growth rate and high malignant potential. This could potentially underestimate the CRC risk associated with serrated polyps left in situ and bias our conclusion that the CRC risk may not be related to the polyp itself.

Finally, our results might be affected by the initial classification of the study groups. Individuals with both large serrated polyps and advanced adenomas were categorized in the advanced adenoma group. This decision was made *a priori.* The rationale for this classification was that an advanced adenoma is a well-known risk factor for CRC, and we did not want our estimates of CRC risk in the serrated polyp group to be confounded by the presence of these well-established high-risk lesions. As a result, our estimates of CRC risk in the serrated polyp group might be too conservative, resulting in a statistically non-significant difference in CRC incidence in the serrated polyp group compared to the general population (NORCCAP control arm, HR 2.5, 95% CI 0.8-7.7). If all individuals with large serrated polyps were included in the serrated polyp group (including those with concurrent advanced adenomas), the HR for CRC incidence compared to the general population would be 3.2 (95% CI 1.3-7.7). The interpretation of the latter result is perhaps

more meaningful than the former: Compared to the general population, the HR for CRC incidence in the presence of a large serrated polyp is 3.2 (95% CI 1.3-7.7), while the HR for CRC incidence in patients with a large serrated polyp without concomitant advanced adenoma is 2.5 (95% CI 0.8-7.7). One could argue that the HR of 3.2 is confounded by the presence of concomitant advanced adenoma, which may indeed be true, but we show that a large serrated polyp is an independent risk factor for CRC when we take characteristics of concurrent adenomas into account (Table 5 in paper II: Odds ratio 3.3, 95% CI 1.3 – 8.6).

## *7.5 Colonoscopy with magnetic endoscopic imaging*

Colonoscopy is the gold standard for follow-up of a positive CRC screening test. The procedure may be uncomfortable or even painful,[129] and fear of pain has been reported as a barrier to CRC screening recommendation adherence.[130] In many countries, colonoscopies are performed with sedation and/or analgesia.[131,132] Sedation, however, has some disadvantages including need for an escort, absenteeism from work, postprocedure activity restrictions and sedation-related complications.[133,134] Sedation-free colonoscopy is without these disadvantages, but to perform unsedated colonoscopy, the proportion of painful procedures should be minimal. In paper III, we conducted a randomized trial to investigate whether the use of a magnetic endoscopic imaging device (MEI) is beneficial to standard colonoscopy using fluoroscopy on demand, which in our institution is standard procedure. A number of studies have investigated the effect of the magnetic endoscopic imaging device.[71,75,76,78,79,135-137] Only one of these studies compared MEI to fluoroscopy on demand.[79] The other trials compared MEI to no external imaging.

Pain reported the day after the colonoscopy was our primary outcome in the trial, measured on a four point Likert scale by the patient. We dichotomized pain; severe pain versus no/slight/moderate pain. We did not find any difference in perceived pain between the MEI colonoscopy arm and the standard colonoscopy arm. This is consistent with most other MEI trials, but two trials showed lower pain scores among experienced endoscopists in favor of the MEI.[76,79] However, in one of these trials, this was a subgroup analysis.[76] In the other trial, the investigators did not detect any difference between the study arms when pain was dichotomized into no/slight vs moderate/severe, while they found a statistically significant difference between the trial arms when scores from a

visual analogue scale (VAS) was used.[79] This could be due to the observation that VAS is more sensitive instrument than a 4 point Likert scale.[138]

We did not find any difference in caecal intubation rate for experienced and inexperienced endoscopists combined. In a systematic review, the use of MEI was associated with an improved caecal intubation rate, OR 1.92 (95% CI 1.13-3.27).[139] This result was mostly due to one study in which the caecum intubation rate was as low as 74% in the control arm.[76] In our trial, the caecum intubation rate was 89.5% in the control arm which implies that a statistically significant positive effect on caecum intubation rate was more difficult to achieve. We would have to include about 3,500 patients in each arm to have 80% power to detect a statistically significant difference between the control arm with 89% intubation rate and the intervention arm with 91% caecal intubation. We detected a statistically significant improvement in caecal intubation rate when MEI-colonoscopy was compared to standard colonoscopy in inexperienced endoscopists (78% vs 56%). This was also found in one other trial.[76] The finding indicates that MEI may be beneficial in educating new colonoscopists and this conclusion is strengthened by our observation that inexperienced endoscopists had less need for assistant from a senior colleague in the MEI group (18.5% vs 40.0%, p=0.018).

We did not detect any difference in caecul intubation time between the study arms. This is consistent with findings from five other trials,[76-78,135,137] while two studies found shorter caecal intubation time with the MEI.[75,79] There were no differences between the two arms in need for sedation/analgesi in our study. A similar finding was found in three other studies. [75-77]. Only one study showed that MEI was associated with lower doses of sedatives and analgetics.[79]

Our trial of the MEI aided colonoscopy has several limitations. First and most important is the limitation with respect to generalizability. The MEI was compared to colonoscopy with fluoroscopy on demand. Thus, our comparison may not be valid in endoscopy centers in which fluoroscopy is unavailable for the colonoscopist. Second, we performed our trial in unsedated patients. If all colonoscopies were conducted with sedation, the endoscopist would have to pay less attention to performing a painless procedure, and caecal intubation failure due to pain would probably be fewer. This might have resulted in more equal caecal intubation rates in the two study arms, especially for the inexperience colonscopists. Third, our trial was a single center trial, and it was unblinded. Both the

endoscopist and the patient may have been affected by the awareness of the "new equipment". Fourth, the feed-back questionnaire from the patient was not anonymous. This may have caused a "please the doctor" effect and the patient may have indicated better pain scores than what was really the experience. However, this would affect the pain scores in both groups to the same extent and should not bias our effect estimate. Fifth, we did not state in the protocol the threshold for introducing fluoroscopy in the standard colonoscopy arm. Because the trial was unblinded, and the outcome was known to the endoscopists, a lower threshold for use of fluoroscopy may have occurred. However, in our trial, fluoroscopy was used in 39% of examinations which is in line with results from 6 other Norwegian hospitals (25.1% to 60.1% of colonoscopies performed with fluoroscopy) in the same period (2007-2010) as our trial.[80] Sixth, three of the endoscopists in our trial were very experienced, having performed more than 5000 colonoscopies each. It may be that their endoscopy technique was firmly established and less influenced by the new equipment. Finally, there is a limit to what extent one may improve one's colonoscopy performance. If the performance is already excellent, as it indeed was for one of the experienced endoscopists in our trial who performed 38% of the examinations in the standard group with a caecal intubation rate of 100%, a difference between the groups will be difficult to uncover.

# 8 Conclusions

- We conclude that screening with flexible sigmoidoscopy offered at one occasion only reduces both the number of new colorectal cancers and deaths from colorectal cancer. We show that also for individuals aged 50-54 years, screening with flexible sigmoidoscopy reduces colorectal cancer incidence.

- The addition of a once only faecal occult blood test to flexible sigmoidoscopy screening does not lead to larger reduction in CRC incidence or CRC mortality compared to flexible sigmoidoscopy screening only.

- Individuals with large serrated polyps in the colon or rectum comprise a high-risk group for developing colorectal cancer. The risk is increased 4.2-fold compared to individuals without polyps at flexible sigmoidoscopy.

- Individuals with large serrated polyps have a risk of colorectal cancer that is comparable to the risk in individuals with advanced adenomas.

- Large serrated polyps may have an indolent course with minimal growth when followed for more than ten years. The polyps may not infer a colorectal cancer risk *itself*, but may be a marker for an excess cancer risk.

- Colonoscopy with the aid of a magnetic endoscopic imager is not less uncomfortable than colonoscopy with fluoroscopy on demand.

- Magnetic endoscopic imaging may be advantageous for inexperienced colonoscopists, leading to higher caecal intubation rate and less need for assistance from a senior colleague.

# 9 Future studies/perspectives

After 11 years, a once only flexible sigmoidoscopy examination is protective with respect to a diagnosis of colorectal cancer and death from colorectal cancer. It will be interesting to follow the NORCCAP cohort, as well as the cohorts in the other flexible sigmoidoscopy trials, to assess for how long this protective effect may last.

For now, it is unknown how often, if ever, a flexible sigmoidoscopy screening examination should be repeated. This can only be properly investigated through a randomized controlled trial in which individuals are randomized to different screening intervals. It is doubtful that such a trial will ever be conducted, even if a roll-out of a national screening program with be an ideal scenario for this study. Indeed, comparative effectiveness trials in cancer screening programs may be feasible and provide adequately powered trials which can answer important research question.[140]

Whether CRC screening should or should not be implemented in Norway is a political decision which has to take effect of the intervention, complications, costs and available resources into account. In Norway, there are no available endoscopy resources which can be allocated for screening purposes. The time from referral until appointment for colonoscopy has been reported to be 100 weeks at one large Norwegian University hospital.[141] We should not put ourselves in a position where we screen asymptomatic individuals for CRC while examination of individuals with symptoms of CRC is postponed due to lack of endoscopic capacity. For this reason, CRC screening should not be implemented in Norway at the present time. We should aim at educating more endoscopists to be able to introduce CRC screening in Norway. Introduction of the Magnetic Imager device may make colonoscopy learning easier. Most cost-effectiveness-studies show that CRC screening is cost-effective, and some suggest that screening may even be cost-saving. This is of great importance for the society, but reducing CRC incidence and mortality is of course even more important for the individual.

If CRC screening should be implemented in Norway, which test to use is also a difficult question. We know from randomized controlled trials that FOBT screening with guaiac based tests reduce CRC mortality, but not CRC incidence, while flexible sigmoidoscopy screening reduces both incidence and mortality. Observational studies consistently shows that also colonoscopy reduces CRC incidence and mortality. I do not think that a test that does not reduce CRC incidence should be implemented in Norway, and guaiac-based

FOBT will probably be abandoned in western countries. Whether the new faecal immunochemical occult blood test with their higher sensitivity for colorectal adenomas than the guaiac-based tests may also reduce CRC incidence is unknown and should be investigated. Finally, new screening tests are evolving and should be compared in randomized trials. Recently, the US Food and Drug Administration approved a stool-DNA test for CRC screening,[142] and blood-testing may be valuable in the future.

To be effective, high compliance with the screening test is necessary and is variable between countries and populations.[143] Accordingly, a test that is suitable in one population may not be the best choice in another. In Norway, we will have sufficient information about adherence to different screening tests in the near future, based both on attendance rates in the NORCCAP trial, from the screening pilot which compares flexible sigmoidoscopy to faecal testing, and from the NordICC trial in which colonoscopy is compared to no screening.

The importance of serrated polyps has just been acknowledged, and much research is needed in this area. Some investigators claim that hyperplastic polyps are without malignant potential, while others propose them as possible ancestors to SSA/P, which are generally acknowledged as cancer precursors. Establishing whether hyperplastic polyps may be SSA/P precursors will be of importance when surveillance recommendations are given. Further, surveillance intervals are unknown for individuals with serrated polyps. This should be investigated through randomized controlled trials with individuals randomized to different surveillance intervals.

We propose that the risk of CRC is as high in individuals with large serrated polyps as in those with advanced adenomas. Our results might be hampered by small numbers and will have to be confirmed in larger trials.

Until now, surveillance recommendations are based on separate consideration of adenomatous and serrated polyps. As serrated polyps seem to be associated with multiplicity of both adenomas and serrated polyps, the total polyp burden may be an important consideration of future risk of CRC. This issue is important, may have an impact on surveillance recommendations, and should be addressed in future trials.

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# 11 Corrections

1. The numbers in the parentheses in paper I, table 4 are per 1,000, not per 100. The sum of advanced CRC in the screening group is 121, not 120. The sum of unclassified CRC in the screening group is 15, not 16. The correct table is displayed below. Corrections in bold:

| | Screening group n (per **1,000**) | | | | Control group |
|---|---|---|---|---|---|
| | | Compliers n=12,955 | Noncompliers n=7,617 | Total n=20,572 | n=78,220 |
| Stage | Screen detected | Post-screen detected | | | |
| Localized | 29 (2.2) | 48 (3.6) | 40 (5.4) | 117 (5.7) | 470 (6.7) |
| Advanced | 10 (0.8) | 49 (3.7) | 62 (8.3) | **121 (5.9)** | 562 (7.8) |
| Unclassified | 2 (0.1) | 4 (0.3) | 9 (1.2) | **15 (0.7)** | 54 (0.8) |
| Total | 41 (3.1) | 101 (7.6) | 111 (15.0) | 253 (12.3) | 1,086 (15.3) |

2. The number needed to screen to save one CRC case is 455 (paper I).

3. The number needed to screen to save on CRC death is 1667 (paper I).